The Pharmaceutical Industry Tussles Over Biosimilars

Federal and State Decisions Will Have a Big Impact on Pharmacists

Stephen Barlas

Calling it a "biosimilar brawl" would be overstating the fireworks, which were exclusively verbal and lacking in venom. But sitting two seats away from one another at a Federal Trade Commission (FTC) workshop on February 5, 2014, biotech executives Bruce Leicher and Geoffrey Eich sparred, a bit heatedly, over whether pharmacists should have to notify physicians when pharmacists substitute an interchangeable biosimilar for the innovator biologic.

Notification is a big and controversial issue as the Food and Drug Administration (FDA) gets ready to approve the first biosimilars for sale in the U.S. Congressional legislation allowing the FDA to consider biosimilars via abbreviated applications was passed as part of the Patient Protection and Affordable Care Act (PPACA). That was four years ago. Since then, the FDA has slowly been publishing draft guidances on what it would expect from companies using this abbreviated approval pathway.

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The Biologics Price Competition and Innovation Act (BPCIA), which was part of the PPACA, did not address notification. That is up to individual states under pharmacy practice statutes. But states are not waiting for the FDA to approve the first biosimilars before establishing laws on notification. Potential impediments to patient access posed by some of those laws worry biosimilar supporters, including the FTC.

Small, struggling biotech companies, such as Momenta Pharmaceuticals, oppose notification. Bruce Leicher, JD, is Senior Vice President and General Counsel at Momenta, which lost $108 million in 2013 and has two biosimilars in development, one in conjunction with Baxter.

Large branded companies, some with patented biologics, such as Amgen, support notification. Geoffrey Eich, MBA, is Executive Director for Research and Development Policy at Amgen, which earned a tad over $5 billion in 2013 on, among other products, branded biologics such as Aranesp (darbepoetin alfa), Enbrel (etanercept), and Epogen (epoetin alfa).

Leicher argues that Amgen and allies such as Novartis/Sandoz, Hospira, Actavis, Boehringer Ingelheim, AbbVie, Genentech, and Lilly are pushing notification at the state level so that they will have "a forum for disparaging comments which can be made without the risk of enforcement." Even though some of those companies also market biosimilars—Hospira's erythropoietin biosimilar Retacrit is a big seller in Europe, for example—Leicher says they are fine with notification because they have large sales and marketing arms that reach deep into physicians' offices.

Eich retorts that passing biosimilars off as generics is "increasingly disparaged by academia, regulators, and competitors as misleading. They have to be foisted on patients, switched at a pharmacy before administration." Biosimilars are not exact copies of biologics. They cannot be, given the way biologics are made: in cell cultures, using a much different and variable manufacturing process than the more precise, cookbook method for making generic copies of small-molecule drugs. But biosimilars are generics in a general, conceptual way.

Biosimilar issues also divide pharmacists. Naming is one of the disputes. The BPCIA did not specify how biosimilars should be identified for purposes of tracking and adverse reaction reporting. This is an issue the FDA will settle, not the states. In Europe, where biosimilars have been legal and sold since 2006, companies identify a product using the International Nonproprietary Name (INN), with both innovator and biosimilar products using the same INN without a suffix. The American Pharmacists Association (APhA) is dead set against using suffixes such as Greek letters (e.g. "alpha") to denote the nonproprietary name of a biosimilar.

The American Society of Health-System Pharmacists (ASHP) thinks that normally it would be sufficient to attach the National Drug Code (NDC) to the INN. That would be suffix enough. But the NDC identifier may not be used to track a product in all settings, and other challenges, such as the reuse of NDC numbers by manufacturers, may make this approach difficult. "Therefore, we do not oppose the addition of suffixes to the INN name if experts believe this approach is needed to facilitate pharmacovigilance," says Christopher Topoleski, ASHP Director of Federal Regulatory Affairs.

Choose any of the controversial biosimilar issues and pharmacists are invariably on the firing line. Some already feel they are dodging metaphorical bullets. First, the push for post-dispensing notification implies that pharmacists are somehow junior, physician-subservient partners in the patient pharmaceutical chain, even though prescription drugs are their full-time business. Marissa Schlaifer, MS, RPh, Head of Policy for CVS Caremark, calls notification "somewhat demeaning" to pharmacists. However, the act of notification won't be that big a deal. To the extent biosimilars are infused in physicians' offices, pharmacists are out of the loop. Biosimilars will be provided in hospital clinics, too, but there pharmacists will have access to electronic medical records and an easy link to the physician. Retail pharmacists will have the biggest challenge if they have to call or fax a physician to note a substitution.

The FTC held the panel on biosimilars to explore whether emerging state laws on biosimilars presented barriers to their use. Any roadblocks could be considered anticompetitive, giving the FTC the authority to intervene. Although some states have already passed laws, they might be premature—a point made by California Governor Jerry Brown when he vetoed a bill in 2013 passed with strong bipartisan support by the California legislature.

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But the FDA will probably approve biosimilars within the next few years, making state laws on notification a very hot topic. Companies like Amgen, Novartis, and Sandoz are on record backing pharmacist notification whenever a pharmacist substitutes either a different patented biologic or a biosimilar for the biologic the physician prescribed. The notification requirement would stay in place until a given state established an interoperable health records system.

Two Biosimilars Categories: Interchangeable or Not

The BPCIA anticipated that the FDA would grant abbreviated approval to biosimilars in two categories: those that are interchangeable with the patented (called "reference") product, and those that are not, which will be referred to as "highly similar." The FDA would first qualify a product as a biosimilar, meaning highly similar. A product deemed biosimilar could still differ in terms of inactive ingredients, purification processes, and other proprietary areas. Therefore, a product that achieves only biosimilarity will not be considered a therapeutic equivalent and will not be eligible for direct substitution without prescriber notification and approval.

The BPCIA allows the FDA to declare a biosimilar interchangeable—and thereby substitutable without a physician's consent—if two conditions are met. The biosimilar must be expected to produce the same clinical result in any given patient, and the risk in terms of safety or diminished efficacy cannot be greater for a switch from a patented to a biosimilar product than continued use of the innovator drug, when the drug is used more than once by the same patient. That is "a pretty high standard," says Phil Katz, a partner with the global law firm Hogan Lovells. "It is not the same as for substitution of small-molecule generic drugs."

The FDA published three draft guidance documents on biosimilars in March 2012. They provided a degree of clarity on some of the methods the agency would use to sort through applications. But specificity on key issues—such as how biosimilars would be named, standards for interchangeability, and other areas—was sorely lacking. Those guidance documents have not been finalized. The FDA says it will publish four more draft guidances in 2014, including one on interchangeability. Marie A. Vodicka, Regulatory Affairs Director for Hogan Lovells, says the FDA does not have to finalize guidance before it can approve a biosimilar application.

Kris Kelly, an FDA spokeswoman, says the FDA's Center for Drug Evaluation and Research (CDER) continues to meet with sponsors interested in developing biosimilar products. As of January 30, 2014, CDER had received 62 requests for initial meetings to discuss biosimilar development programs for 13 different reference products; the FDA had held 53 initial meetings with sponsors. To date, CDER has received 22 investigational new drug (IND) applications for biosimilar development programs, and additional development programs are proceeding under pre-INDs. Twenty-one biologics with a market value of more than $50 billion will lose patent protection by 2019 in the U.S. alone.

While notification was the most controversial issue discussed at the FTC's February workshop, it wasn't the only one. The daylong discussion covered a range of topics, such as how state laws on small-molecule generics had affected uptake of those drugs, how biosimilars should be named, and the associated issue of pharmacovigilance, meaning the tracking of adverse effects, as well as interchangeability.

Europe Is Way Ahead

Given the high cost of most biologics, the potential for lower prices, and the availability of biosimilars in Europe and Asia, there is considerable pressure on the FDA to open the biosimilar floodgates. The European Union (EU) approved the first biosimilar, Omnitrope (somatropin), in 2006. To date, the European Medicines Agency (EMA) has approved 20 biosimilars within the product classes of human growth hormone, granulocyte colony-stimulating factor, erythropoietin, and tumor necrosis factor. Once the EMA approves a product, it is up to an individual country whether to allow sales within its borders. In June 2013, the EMA approved the first monoclonal antibody (mAb) therapies for Johnson & Johnson's Remicade (infliximab). Those are Hospira's Inflectra and Celltrion's Remsima. Sandoz's Zarzio (filgrastim) has become the first biosimilar to overtake both its reference product (Amgen's Neupogen) and European market leader (Chugai's Granocyte).

Eight of the 10 highest-expenditure Medicare Part B drugs in 2010 were biologics. Leigh Purvis, Senior Strategic Policy Advisor for AARP, says the average annual cost of a branded biologic is around $34,550. Costs can run as low as $25,000 and as high as $200,000. Many biologics are infused in a physician's office. If a senior under Medicare Part B receives that drug, he or she is responsible for a 20 percent copayment. If that drug is procured under Part D, Medicare's outpatient drug program, there is a cap of $4,550 for the patient. For nonseniors, PPACA marketplace plans typically put expensive biologics on high tiers with substantial cost sharing, although there, too, caps come into play.

Express Scripts looked at the 11 branded biologics that will lose patent protection over the next decade. Its back-of-the-envelope calculation is that an average 30 percent price discount for the biosimilar could yield a quarter of a trillion dollars of savings in the U.S. for those 11 products during the next decade. That assumes no interchangeability until 2020.

Are States Jumping the Gun?

State laws mandating pharmacist notification or limiting interchangeability could crimp savings to individuals, employers, Medicare, and Medicaid. The FTC's position is that state laws aiming to protect patient safety can restrict the use of biosimilars, but those restrictions should be no broader than necessary to protect legitimate concerns. At the workshop, FTC Chair Edith Ramirez said, "There is substantial uncertainty at the state level surrounding how follow-on biologics will compete with their reference products." Last year, 15 state legislatures considered laws that would affect how pharmacists could dispense interchangeable biosimilars.

Jessica Mazer, Assistant Vice President of State Affairs for the Pharmaceutical Care Management Association, says the most radical state bill (the association opposes state limitations on prescribing interchangeables) was in North Dakota. That state enacted a law that requires a pharmacist to notify a prescriber within 24 hours of substitution. Some states are including provisions allowing substitutions only when a state

has some measure of interoperable electronic health information exchange. Another state legislative permutation is the walling off of some drug categories from interchange, particularly insulin products.

Besides Momenta's Leicher, some other panelists at the FTC workshop had sharp criticism of the proposal by Amgen, Novartis, Hospira, and the others, which Sumant Ramachandra, MD, PhD, MBA, Senior Vice President and Chief Scientific Officer of Hospira, justified on the basis of "transparency."

Amgen's Eich explains, "Absent some level of interoperable health records or after-the-fact communication between pharmacy and clinician's office, the patient's medical record will be rendered either ambiguous or inaccurate."

Leicher says that e-prescribing networks are operational nationally, and physicians already have the capability to access the pharmacy and find out whatever they want to know about a patient and his or her prescriptions. Steven B. Miller, MD, MBA, Senior Vice President and Chief Medical Officer for Express Scripts, agrees. He points out that Surescripts, where he sits on the board of directors, reaches 500,000 physicians, 65,000 pharmacies, and all 5,500 hospitals in the U.S. "We already have a system that is safe and effective," he insists. "Notification is truly unnecessary."

Dr. Miller distinguishes between that current system and an interoperable system that is nowhere in sight. He said physicians offices, hospitals, and pharmacies have about 30 different e-prescribing software systems; that complexity was worsened by the 2009 economic stimulus bill that contained about $19 billion in grants for physicians and hospitals to put software in place. "The current system is immature," he explains. "Some software cannot even express the formulary a patient is on. Interoperability is a fantasy, and we won't have it for a long, long time."

Even some proponents of notification admit the proposal they support has weaknesses. Mark McCormish, MD, PhD, Global Head of Biopharmaceutical Development for Sandoz, admits, "We have tried to come up with language, not that it is perfect or great."

What's in a Name?

How biosimilars should be named is also the subject of substantial controversy. It is an important issue because a physician or pharmacist reporting an adverse reaction to a national health agency or the manufacturer must be able to distinguish the offending drug from others in its class, both branded and biosimilar. In an effort to influence the FDA's position on naming, the Generic Pharmaceutical Association (GPhA) submitted a petition to the FDA in 2013 requesting that the FDA implement its International Nonproprietary Name (INN) policy equally for all biologics. The World Health Organization (WHO) administers the INN system. An INN names the active ingredient, so products sharing the same INN can be readily identified as sharing the same active ingredient. In addition to the INN, a product (including biosimilars) will have other names and identifiers—for example, a brand name and, in the U.S., an NDC, that readily distinguish it from other products that share the same INN. The EU has used INNs to track biosimilars (and brand-name biologics) as part of pharmacovigilance programs.

Underlining how divided the pharmaceutical industry is over multiple biosimilar issues, Novartis, Amgen's ally on notification, supports the GPhA's position. Amgen opposes it.

The BPCIA doesn't address how biosimilars should be named. The subject came up during congressional debate, but no provision was added to the bill. The FDA outlined its naming position for biosimilars in a policy paper sent to the WHO in 2006 in support of the current WHO naming conventions. In its 2006 paper, the GPhA's petition states, the FDA "agrees that there should be no change in global policy and rejects distinctive INN designations for biosimilars."

In a response to the GPhA petition, Paul R. Eisenberg, MD, MPH, FACP, FACC, Senior Vice President of Global Regulatory Affairs and Safety at Amgen, says the GPhA cites only a portion of the FDA's 2006 policy paper but omits the remainder of the context. "We believe that the best solution is that the reference product and biosimilar should share a root and have distinct suffixes," he adds. Greek letters, such as alpha, beta, or gamma, or the manufacture's name could serve as the distinct suffix. Examples of the resulting name would be "supermab alpha" or "supermab Amgen." This is similar to the naming convention employed by the Japanese regulatory authority, Dr. Eisenberg states.

The reason Amgen and others believe biosimilars deserve unique, nonproprietary names is that unlike chemically synthesized drug products, no two biological products are identical. Small differences can have significant and unpredictable effects on patients' immune responses. The companies also argue that the inability to disaggregate safety information could lead to significant safety risks.

But Alan M. Lotvin, MD, Executive Vice President of Specialty Pharmacy for CVS Caremark, says a unique suffix, for example, would "confuse the role of the nonproprietary name." He argues that biosimilars approved in Europe and elsewhere have the same INN as their reference drug with no evidence of safety problems. Different nonproprietary names would discourage states from allowing substitution even if the FDA has designated the biosimilar as interchangeable. "The different nonproprietary name will be used to suggest that the active ingredients in the two medicines are different," he states.

The APhA has also weighed in against the use of suffixes. During an FDA workshop on the first set of draft guidance in May 2012, Marcie Bough, PharmD, then Senior Director of Government Affairs with the APhA, said suffixes present challenges for pharmacy operating systems and in processing for fulfilling orders. Suffixes may not be included in the original electronic or written prescription. They may fall off the electronic drop-down menu order form for product selection, and they may not fit into the data field in the database. Michelle Spinnler, an APhA spokeswoman, says that continues to be the group's position.

The ASHP also sees potential problems with suffixes, though it sees problems, too, with unique names. "Unique INNs would complicate the collection of product safety data across the industry," notes Topoleski. "Unique INNs would make U.S. product names different than those in the rest of the world and such a policy would be contrary to the World Health Organization naming system." The ASHP therefore wouldn't oppose suffixes such as Greek letters, but it would oppose prefixes.

Patient groups are something of a wild card in the biosimilar

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debate. On the one hand, they want cheaper biosimilars. On the other hand, they want assurance that those interchangeable and highly similar biosimilars are as safe and effective as the reference drug, and right for the patient.

Marcia Boyle, President and founder of the Immune Deficiency Foundation, wants the FDA to prohibit immunoglobulin therapies from being interchanged, at least until the science advances significantly. She bolsters her case by referring to Octapharma USA's worldwide voluntary withdrawal in 2010 of 31 lots of Octagam intravenous human immunoglobulin 5% as a result of an increased number of reported adverse events. "Unlike generic drugs, biosimilars can never be identical copies of a reference product," she states. "The choice of product should not be determined by a pharmacist, regulator, or insurer, but by a physician in consultation with his/her patient."

It is impossible to predict how the debates over notification, interchangeability, and naming will turn out. But given the overwhelming success of small-molecule generics since the Hatch-Waxman Act was passed in 1984, it is hard to imagine that either the FDA or the states will substantially stymie biosimilar access. ■